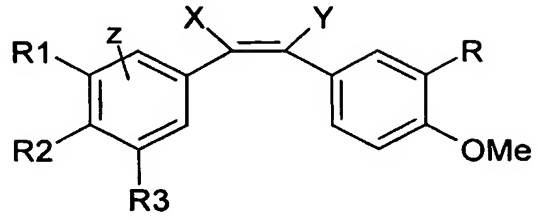
CLAIMS

1. A compound of formula (I)



wherein:

R_1, R_2 and R_3, which can be the same or different, are H, OMe, NO_2, NHR';

X and Y, different each other, are halogen or H;

Z = H or halogen

R = OH, OPO_3Na_2, $OCH_2OPO_3Na_2$, OR', NO_2, NHR';

R' = H, alkyl (C_1-C_6), $(COCHR"NH)_n$-H;

R" = H, an amino acid side chain, Ph;

n an integer comprised between 1 and 3;

their pharmaceutically acceptable salts, racemates and single enantiomers.

2. A compound according to Claim 1, selected from the group consisting of:
a compound wherein at least one of X and Y is halogen, R_1-R_3 are methoxy, and R is hydroxy;
a compound wherein at least one of X and Y is halogen, R_1-R_3 are

methoxy, R is amino or substituted amino;
a compound wherein at least one of X and Y is halogen, R_1-R_3 are different from methoxy, R is hydroxy;
a compound wherein R is OPO_3Na_2 and
a compound wherein R' is $(COCHR"NH)_n$-H.

3. A compound according to Claim 1 or 2, wherein R" is the side chain of a natural amino acid.

4. A compound according to Claim 1 selected from the group consisting of:
X = Y = F; R = OPO_3Na_2: difluorocombretastatin;
X = Y = F; R = NH_2: difluoroaminocombretastatin;
X = H; Y = F; R = OPO_3Na_2: monofluorocombretastatin;
X = F; Y = H; R = OPO_3Na_2: monofluorocombretastatin;
X = H; Y = F; R = NH_2: monofluoroaminocombretastatin;
X = F; Y = H; R = NH_2: monofluoroaminocombretastatin.
X= Br; Y=F; R= OPO_3Na_2 bromofluorocombretastatin

5. A process for the preparation of the compounds of Claim 1, wherein X and Y are both F comprising the following steps:
a) reaction of 1-bromo-1,2-difluoro-2-(4-methoxy-3-(protected OH)-phenyl)ethene with 3-R_1-4-R_2-5-R_3-phenylboronic acid, and
b) restoring the 3-(protected OH) group.

6. A process for the preparation of compounds of Claim 1, wherein one of the X and Y is F and the other one is hydrogen, comprises the following steps:
a) bromofluorination of the compound of Formula (I), wherein X and Y are H, and
b) base-promoted HBr elimination.

7. A process for the preparation of compounds of Claim 1, wherein one of the X and Y is F, comprising the following steps:
a) transformation of compound of Formula (I), wherein X and Y are

H into the respective bromohydrin, and
b) base-promoted HBr elimination.

8. A process for the preparation of compounds of Claim 1, wherein one of the X and Y is F, comprising the following steps:
a) transformation of compound of Formula (I), wherein X and Y are H into the respective epoxide;
b) epoxide opening to give the respective bromohydrin, and
c) base-promoted HBr elimination, or in alternative,
d) epoxide opening to give the respective fluorohydrin, and
e) elimination of the opportune hydroxyl derivative.

9. A process for the preparation of compounds of Claim 1, wherein one of the X or Y is F and the other is Br, comprising the following steps:
a) transformation of compound of Formula (I), wherein X and Y are H into the respective bromohydrin, and
b) base-promoted HBr elimination.

10. The use of the compounds of any one of Claims 1-4 for the recognition and binding to the tubulin site.

11. The use of the compounds of any one of Claims 1-4 as medicaments.

12. The use of the compounds of any one of Claims 1-4 for the preparation of a medicament for treating a pathological state.

13. The use according to Claim 12, wherein said pathological state is a tumour.

14. The use according to Claim 13, wherein said tumour is selected from the group consisting of sarcoma, carcinoma, carcinoid, bone tumour, neuroendocrine tumour, lymphoid leukaemia, acute promyelocytic leukaemia, myeloid leukaemia, monocytic leukaemia,

megakaryoblastic leukaemia and non Hodgkin's disease, hemangiomas and multiple myeloma, anaplastic thyroid cancer.

15. Use of compounds, according to claim 5, as antimetastatic agents.

16. The use according to Claim 12, wherein said pathological state is caused by abnormal angiogenesis.

17. The use according to Claim 16, wherein said pathological state caused by abnormal angiogenesis is selected from the group consisting of tumour metastases; arthritic disease; diabetic retinopathy; macular degeneration, psoriasis; chronic inflammatory diseases or arteriosclerosis.

18. The use according to Claim 12, wherein said pathological states is a non-neoplastic disease.

19. A pharmaceutical composition comprising at least a compound of any one of Claims 1-4, in admixture with at least one pharmaceutically acceptable carrier and/or excipient.

FIGURE 1

Scheme 1: synthesis of difluorocombretastatin

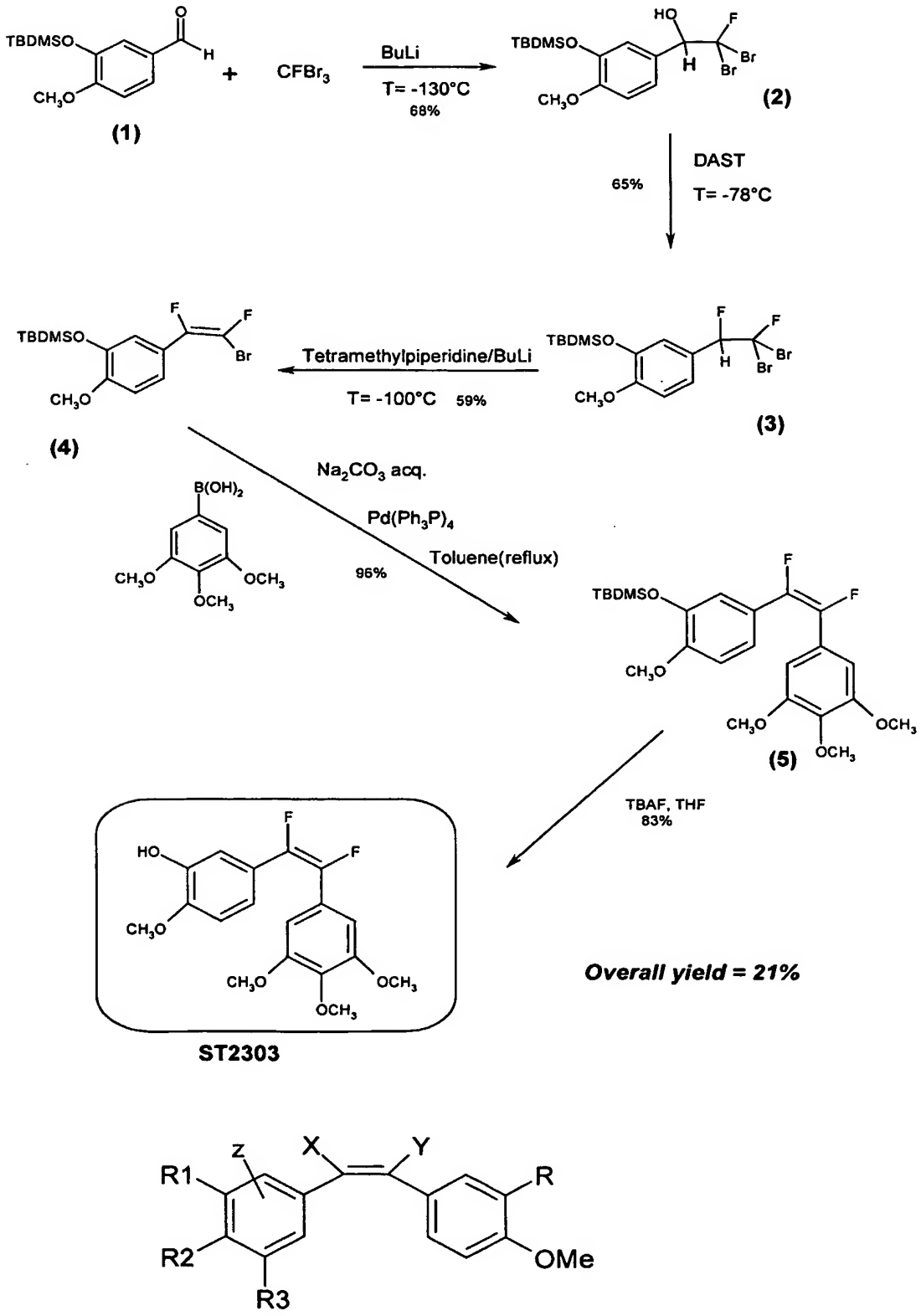


FIGURE 2

Scheme 2: Synthesis of difluoro-Nitro- and difluoro-Amino-combretastatin

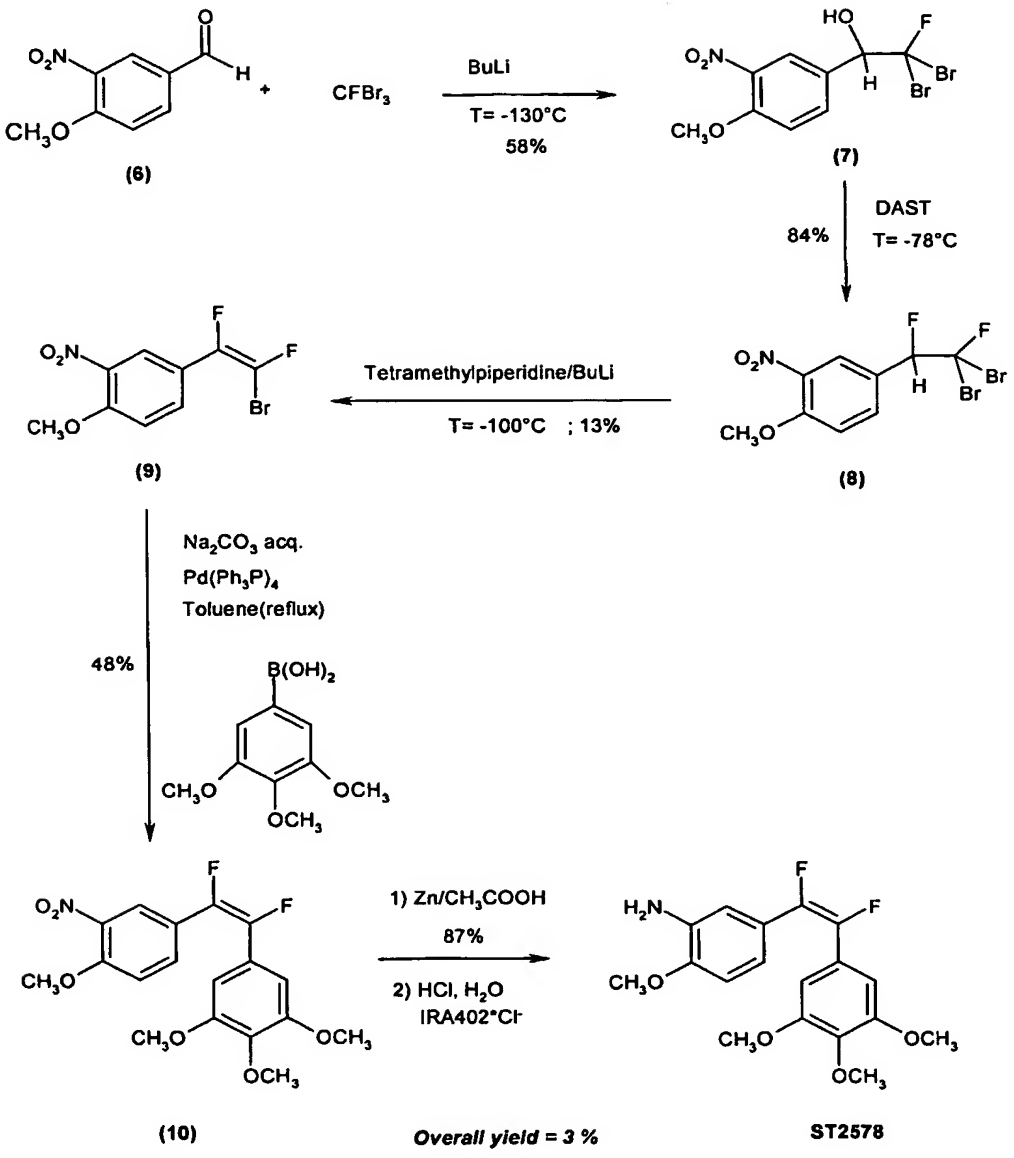
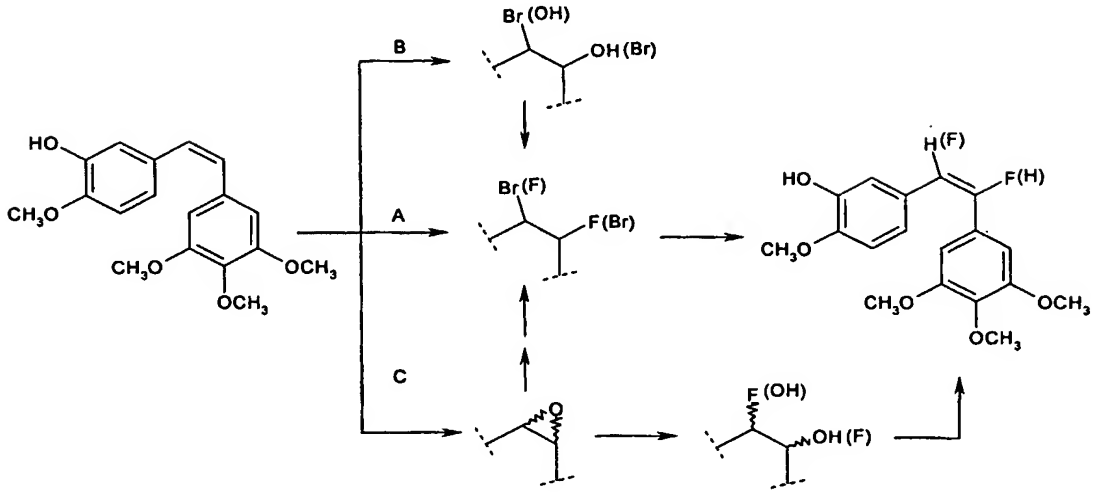


FIGURE 3

Scheme 3: Synthesis of monofluorocombretastatins



Scheme 3a: Total synthesis approach to monofluorocombretastatin

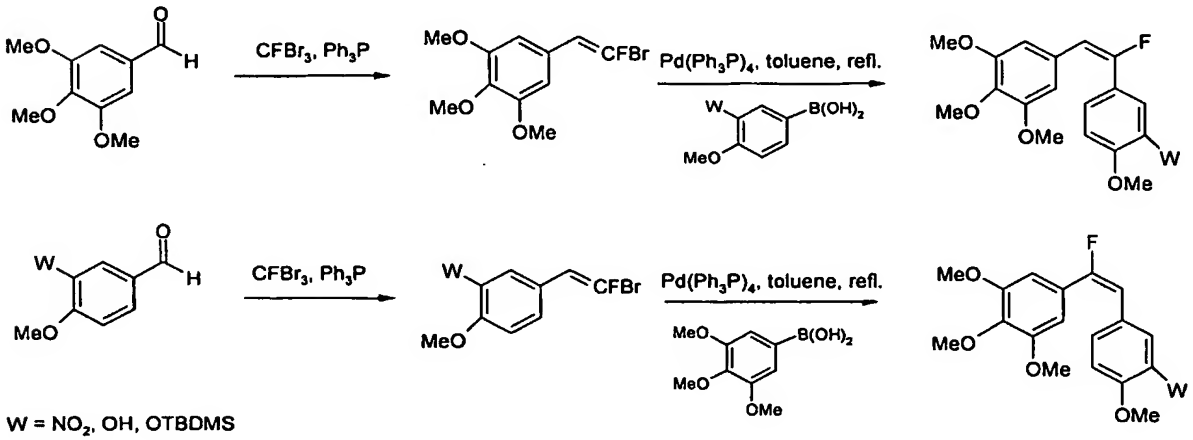
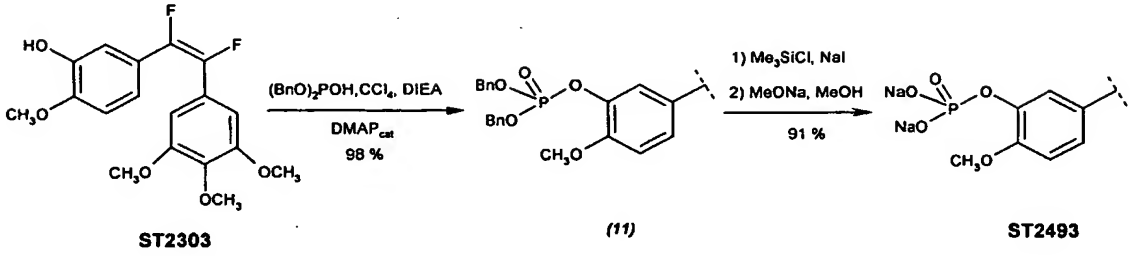


FIGURE 4

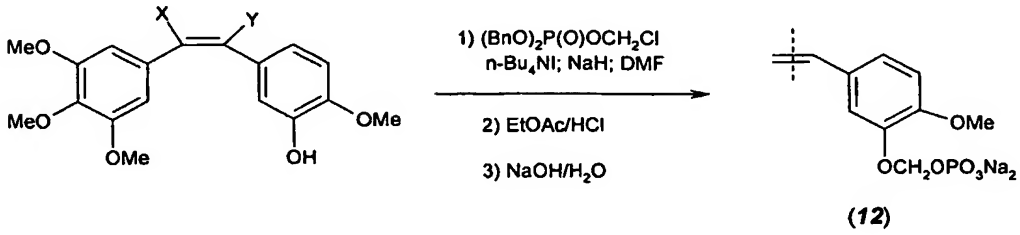
Scheme 4: Synthesis of disodium-phosphate prodrug difluoro-combretastatin (ST2493)



ST2303 (11) ST2493

FIGURE 5

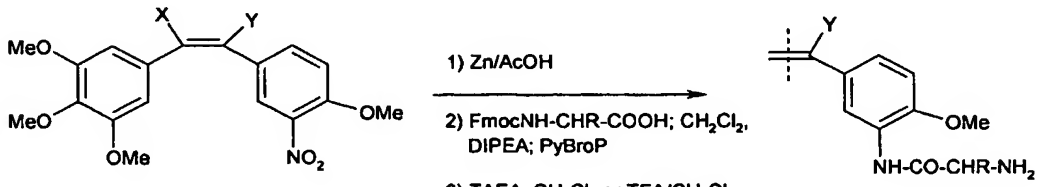
Scheme 5: Synthesis of disodium mono-difluorocombretastatin-4-O-methyloxyphosphate [12]



(12)

FIGURE 6

Scheme 6: General Procedure for obtaining amide derivatives [13].



(13)

FIGURE 7

Scheme 7: Synthesis of bromofluorocombretastatin